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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-01018
Patent 9,114,166 B2

Before RAMA G. ELLURU, TINA E. HULSE, and
ELIZABETH A. LAVIER, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Coherus Biosciences Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–4, 6–10, 13–16, 23–26, and 28 of U.S. Patent No. 9,114,166 B2 (Ex. 1001, "the '166 patent"). Paper 1 ("Pet."). AbbVie Biotechnology Ltd. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 9 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petition and Preliminary Response, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–4, 6–10, 13–16, 23–26, and 28 of the '166 patent. Accordingly, we deny the Petition and decline to institute an *inter partes* review.

A. Related Proceedings

The '166 patent is part of a family of continuation applications originating from U.S. Patent Application No. 10/222,140. Pet. 8; Paper 8, 1. The parties do not identify any litigation involving the '166 patent.

Amgen, Inc. filed petitions for *inter partes* review challenging certain claims of related U.S. Patent Nos. 8,916,157 B2 and 8,916,158 B2 in IPR2015-01514 and IPR2015-01517, respectively. Pet. 8; Paper 8, 1–2. The Board denied both petitions. *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, Case IPR2015-01514, slip op. at 24 (PTAB Jan. 14, 2016) (Paper 9) ("-1514 Dec."); *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, Case IPR2015-01517, slip op. at 26 (PTAB Jan. 14, 2016) (Paper 9) ("-1517 Dec.").

B. The ’166 Patent

The ’166 patent is titled “Formulation of Human Antibodies for Treating TNF-α Associated Disorders.” Ex. 1001, at [54]. Tumor necrosis factor alpha (“TNF-α” or “TNFα”) is a cytokine implicated in various diseases and disorders in humans, including sepsis, autoimmune diseases, and transplant rejection. *Id.* at 1:39–52. Thus, TNFα is a target for various therapeutic strategies, including antibodies that bind to and neutralize TNFα, to counteract or inhibit its activity. *Id.* at 1:57–61. Accordingly, the ’166 patent states that there is a need for a stable aqueous pharmaceutical formulation with an extended shelf life, comprising an antibody that is suitable for therapeutic use to inhibit or counteract detrimental TNFα activity. *Id.* at 3:14–17. The ’166 patent further states that there is a need for a stable, aqueous pharmaceutical formulation with an extended shelf life comprising an antibody suitable for therapeutic use that is easily administered and contains a high protein concentration. *Id.* at 3:17–21.

C. Illustrative Claim

Petitioner challenges claims 1–4, 6–10, 13–16, 23–26, and 28 of the ’166 patent, of which claim 1 is the only independent claim. Claim 1 is representative and is reproduced below:

> 1. A stable liquid aqueous pharmaceutical formulation comprising: a human anti-human Tumor Necrosis Factor alpha (TNFα) IgG_1 antibody at a concentration of 50 mg/ml, wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7, and a buffer system;
>
> wherein the formulation is isotonic, suitable for single-use subcutaneous injection, and has a pH of 4.0 to 8.0.

D. The Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–4, 6–10, 13–16, 23–26, and 28 of the '166 patent on the following ground:

References	Basis	Claims challenged
van de Putte[1] and Relton[2]	§ 103	1–4, 6–10, 13–16, 23–26, and 28

Petitioner also relies on the testimony of Mark C. Manning, Ph.D. (Ex. 1002).

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that as of August 16, 2002, a person of ordinary skill in the art would have had "an advanced degree in biology, biochemistry, or chemistry (or a related discipline)," and "would have had at least two years of experience preparing stable formulations of proteins suitable for therapeutic use." Pet. 16 (citing Ex. 1002 ¶ 42). Patent Owner does not contest the level of ordinary skill in the art. Prelim. Resp. 8.

On this record, we adopt Petitioner's uncontested definition of the level of ordinary skill in the art. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not

[1] L.B.A. van de Putte et al., *Six Month Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 59 Annals of the Rheumatic Diseases Supp.1 (2000) (Ex. 1007).
[2] Julian Marcus Relton, US 6,252,055 B1, issued June 26, 2001 (Ex. 1006).

shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *In re Cuozzo Speed Techs., LLC*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "stable"

Claim 1 recites a "stable liquid aqueous pharmaceutical formulation" in the preamble of the claim. Petitioner states that if the Board decides the preamble is a limitation and the construction of "stable" is necessary, then it should be construed as it is defined in the '166 patent as a formulation "in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage." Pet. 17 (quoting Ex. 1001, 7:24–65). Petitioner continues, stating that this definition "reflects that the IgG_1 antibody is sufficiently stable in a liquid formulation administered subcutaneously to a human such that the formulation is biologically effective and not significantly toxic." *Id.* (citing Ex. 1001, 7:15–23). Patent Owner contends that the term "stable" should be construed

consistently with our decisions in the prior *Amgen* IPRs and as "requiring stability for storage and use as a liquid aqueous pharmaceutical product." Prelim. Resp. 8.

As an initial matter, we determine that the preamble is limiting for the same reasons stated in our prior *Amgen* decisions. *See, e.g.*, -1517 Dec. 6–7. That is, based on the '166 patent as a whole, we determine that the phrase "stable liquid aqueous pharmaceutical formulation" breathes life and meaning into claim 1 and, therefore, limits its scope. *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) ("[A] preamble limits the invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim.'") (citation omitted).

Regarding the meaning of "stable" in the context of a "stable liquid aqueous pharmaceutical formulation," we do not ascertain a substantive difference between the parties' respective definitions. Both parties agree that the formulation must be sufficiently stable for use when administered subcutaneously to a human. Having reviewed the record and the arguments of the parties, we see no reason to deviate from our prior construction of the term "stable" in the related patents. *See, e.g.*, -1517 Dec. 7–8. In other words, we construe "stable" to mean "a formulation in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage and use as a pharmaceutical formulation."

2. Remaining Claim Terms

Notwithstanding any alleged differences between the parties' proposed constructions for the remaining terms, we determine that it is unnecessary to expressly construe these claim terms for purposes of this

Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Obviousness over van de Putte and Relton

Petitioner asserts that claims 1–4, 6–10, 13–16, 23–26, and 28 of the '166 patent are unpatentable as obvious over van de Putte and Relton. Pet. 32–54. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 29–61. On this record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing any of the claims are unpatentable based on the combined teachings of van de Putte and Relton.

1. van de Putte (Ex. 1007)

van de Putte is an abstract describing a dose-finding phase II study comparing three dose levels of D2E7 administered to patients with long-standing active rheumatoid arthritis. Ex. 1007, 2. The patients received weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous injection for three months. *Id.* After three months, the patients receiving the placebo were given 40 mg D2E7 weekly for three months while all other patients' doses remained the same. *Id.* The investigators concluded that all three doses were superior to the placebo, and were equally efficacious. *Id.*

2. Relton (Ex. 1006)

Relton relates to pharmaceutical formulations containing a concentrated antibody preparation. Ex. 1006, 1:6–9. Relton teaches a monoclonal antibody preparation for administration to a human, where the recombinant antibody is at a concentration of preferably 100 mg/ml or greater. *Id.* at 3:1–5. Relton also teaches that the invention is applicable to all classes of immunoglobulins, and is preferably applied to IgG

immunoglobulins, including most preferably IgG_1. *Id.* at 3:19–27. According to Relton, subcutaneous formulations according to the invention are preferably isotonic and will generally range from pH 4–9. *Id.* at 4:24–27. Relton also discloses various subcutaneous formulations for Anti-CD4 and Anti-CD23 antibodies in Example 4. *Id.* at 11:51–12:22.

3. Analysis

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Petitioner argues that "the ***only*** difference between the formulation components in Example 4 (formula b) [of Relton] and the challenged claims is the presence of a different IgG_1 antibody, as opposed to the IgG_1 antibody D2E7." Pet. 30. Petitioner then relies on van de Putte for its teaching of D2E7. *Id.* at 33. Petitioner argues that it was well known that D2E7 effectively treated rheumatoid arthritis when administered as a weekly dose of 20, 40, or 80 mg D2E7 by subcutaneous self-injection. *Id.* Petitioner further argues that a person of ordinary skill in the art would have had a reason to prepare a stable liquid formulation of D2E7 with a buffer system because liquid formulations were the preferred form of delivering proteins due to the convenience of manufacturing and clinical use. *Id.* According to

Petitioner, the prior art also taught that it was preferable to deliver the dose of D2E7 in a single subcutaneous injection having a volume between 0.5 ml and 1.0 ml. *Id.* at 34. Relying on that assumption, Petitioner concludes that van de Putte teaches administering a range of D2E7 concentrations between 20 mg/ml and 160 mg/ml. *Id.* (citing Ex. 1002 ¶¶ 74, 151–157).

Petitioner further argues that any difference between Relton and claim 1 is irrelevant because Relton teaches the formulation for the entire IgG_1 subclass, which includes D2E7. *Id.* at 35 (citing Ex. 1006, 3:26–27, Example 4; Ex. 1002 ¶ 118). Petitioner contends that "a [person of ordinary skill in the art] would not have thought formulating D2E7 with a buffer system *as the only specified requirement* posed any special challenges compared to other IgG1 antibodies." *Id.* (citing Ex. 1002 ¶¶ 128–129). Accordingly, Petitioner concludes that a person of ordinary skill in the art "would have had a reasonable expectation of success based on the teaching of van de Putte that stable, liquid formulations of D2E7 for single-use subcutaneous dosing had already been made and used in patients." *Id.* at 49. According to Petitioner, the combination of van de Putte and Relton is nothing more than "the predictable use of prior art elements according to their established functions." *Id.* at 49–50 (quoting *KSR*, 550 U.S. at 417).

Having considered the arguments and evidence, we are not persuaded that Petitioner has shown sufficiently that the subject matter of the challenged claims of the '166 patent would have been obvious over the cited prior art. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention

does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014). Even assuming, as Petitioner asserts, that a skilled artisan reading van de Putte and Relton would have had a reason to combine the references to prepare a stable, liquid formulation of 50 mg/ml D2E7, as required by each of the challenged claims, we are not persuaded on this record that a skilled artisan would have had a reasonable expectation of success in doing so in light of the state of the art at the time.

As an initial matter, we note that van de Putte does not disclose whether the administered D2E7 formulation was in liquid form or lyophilized form. Ex. 1007. Nor does van de Putte teach the concentration of antibody in the formulation, the ingredients of the formulation, or whether it was administered as a single-dose or multi-dose delivery. *Id.* Thus, van de Putte offers no guidance as to how a person of ordinary skill in the art would prepare a stable, liquid formulation of 50 mg/ml D2E7.

Instead, as support for the reason to prepare a liquid formulation, Petitioner relies on the assertion that liquid formulations were "generally preferred due to the convenience of manufacturing and use." Pet. 24 (quoting Ex. 1025,[3] 10[4]). But the same book quoted by Petitioner (and edited by Petitioner's declarant, Dr. Manning) states in the very next

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[3] *Rational Design of Stable Protein Formulations*, 13 PHARMACEUTICAL BIOTECHNOLOGY (John F. Carpenter & Mark C. Manning eds., 2002) (Ex. 1025).

[4] Like the parties, we cite the page numbers of the references rather than the page numbers provided by Petitioner pursuant to 37 C.F.R. § 42.63(d)(2), to avoid confusion.

sentence that "protein drugs may not be stable enough to be handled as a liquid formulation." Ex. 1025, 10. The book then reiterates several times how difficult it is to develop a stable liquid formulation for proteins. *See, e.g.*, *id.* at 10–11 ("It is important to understand that developing conditions to keep proteins stable in a liquid form for a pharmaceutically relevant storage time (e.g., two years) is not a simple task."); 109 ("[W]ith many proteins, it is not possible—especially considering the time constraints for product development—to develop sufficiently stable aqueous formulations.").

Although Dr. Manning admits in his declaration that "development of stable liquid formulations presented certain stability challenges," he contends that "formulators knew how to address them." Ex. 1002 ¶ 86 (citing Ex. 1025). He then discusses the "established and finite set of tools" that a protein formulator could use to address stability issues, including pH selection, excipient selection, and buffer and tonicity agents. *Id.* ¶¶ 90–117.

In the chapter he authored in Exhibit 1025 (Chapter 8), however, Dr. Manning states that "for most proteins[,] maintaining physical and chemical stabilities in aqueous solution for an extended period of time is extremely difficult." Ex. 1025, 184. He also states that "[i]t can be *assumed* that most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed." *Id.* at 188 (emphasis added). Given this uncertainty in the art, we are not persuaded by Dr. Manning's testimony in this proceeding that a skilled artisan would have had a reasonable expectation of success in preparing a stable, liquid formulation of D2E7.

Petitioner also argues that, because the only difference between claim 1 and Relton is that the IgG_1 antibody must be D2E7, a skilled artisan would not have thought formulating D2E7 posed any special challenges

compared to other IgG_1 antibodies. Pet. 35 (citing Ex. 1002 ¶¶ 128–129). Petitioner claims that Relton provides detailed information on how to make stable, liquid formulations with IgG_1 antibody concentrations up to and exceeding 100 mg/ml. *Id.* at 36 (citing Ex. 1002 ¶¶ 130, 158, 159). Moreover, Dr. Manning testifies that a person of ordinary skill in the art would have "had no reason to believe D2E7 would present any particular problems or difficulty in the formulation process relative to other IgG_1 antibodies." Ex. 1002 ¶ 162. He further claims that "by following the general guidance in the art and more specifically the teachings in Relton, a [person of ordinary skill in the art] would have had a reasonable expectation of success in preparing a stable liquid pharmaceutical formulation [according to the claims]." *Id.* ¶ 167. Accordingly, Petitioner asserts that the combination of van de Putte and Relton reflects an obvious solution to a known problem. Pet. 49.

We are not persuaded by this argument and supporting evidence. Petitioner's argument that Relton's disclosure of the class of IgG_1 antibodies is sufficient guidance for a skilled artisan to prepare a stable, high-concentration, liquid formulation of D2E7 is once again belied by the state of the art and Dr. Manning himself. In his book chapter (Chapter 8), Dr. Manning states that "[t]he exquisite sensitivity of protein structure, function, and stability to the primary sequence does not readily lend itself to a generic approach for protein formulation." Ex. 1025, 185. He continues, stating "[e]ven for closely related proteins, the relative stability and major pathways for degradation might be quite different." *Id.* at 185–86. Dr. Manning's opinion (from his book) is consistent with Patent Owner's summary of the

state of the art at that time. *See* Prelim. Resp. 21–25. For example, Wang[5] explains that, although certain factors have been identified that contribute to the stabilization of proteins, "the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." Ex. 1030, 130. Accordingly, Wang concludes that "the most formidable challenge in formulating a liquid protein pharmaceutical is to preserve the biological activity of the protein for an acceptable shelf life. Unfortunately, there is no single pathway to follow in formulating such a product. Usually, proteins have to be evaluated on a case-by-case basis." *Id.* at 178. Thus, we are not convinced by Petitioner's argument that Relton's generic disclosure of IgG_1 antibody formulations translates to a reasonable expectation of success in formulating a stable, liquid, high-concentration D2E7 formulation.

Accordingly, we determine that Petitioner has not shown sufficiently that a skilled artisan—without the benefit of hindsight—would have combined van de Putte and Relton to achieve the claimed formulation with a reasonable expectation of success. *See Grain Processing Corp. v. Am.-Maize Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983))).

[5] Wei Wang, *Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals*, 185 INTL. J. PHARMACEUTICS 129–88 (1999) (Ex. 1030).

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not established a reasonable likelihood of prevailing on its assertion that claims 1–4, 6–10, 13–16, 23–26, and 28 of the ’166 patent are unpatentable as obvious over the combination of van de Putte and Relton.

IV. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner’s request for an *inter partes* review of claims 1–4, 6–10, 13–16, 23–26, and 28 of the ’166 patent is *denied*.

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